Early Programming of Later Health and Disease: Factors Acting During Prenatal Life Might Have Lifelong Consequences

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A slow rate of intrauterine or prenatal growth is known to be a major risk factor for several noncommunicable diseases, including coronary heart disease and type 2 diabetes (1–7). A small body size at birth, markers of which include a low birth weight, thinness, and shortness at birth, is commonly recognized as a manifestation of slow prenatal growth. However, it is not the small body size per se that is the underlying problem, but what it stands for. Programming describes the process when events during critical periods of development may change structure and function of the organism (8). Fetal malnutrition can influence prenatal growth and consequently program later health. Also, other factors, e.g., stress, can influence prenatal growth. Causes of severe prenatal stress include natural and human disasters, such as famines, earthquakes, and terrorist attacks. Studies on the effects on birth outcomes in term deliveries after the World Trade Center attacks in 2001 showed that birth weight in the offspring was significantly lower for those who lived close to the event site (9). Interestingly, fetal programming can also occur without any marked effect on birth size. This has been shown in the Dutch Hunger Winter study, findings from which suggested that malnutrition—and stress—during prenatal life have a long-term effect by increasing the risk of coronary heart disease and type 2 diabetes in later life. These effects also depend upon timing of the exposure (10).

In this issue of *Diabetes*, Li et al. (11) report on the long-term health consequences of exposure to the Chinese famine in early life, with a focus on risk for impaired glucose regulation. The study offers a unique opportunity to study the early programming of health and disease as a consequence of a natural disaster, the Chinese famine from 1959 to 1961, in ~8,000 adults born from 1954 to 1964. The study findings suggest that people who were exposed to the famine while in utero were at higher risk for impaired glucose regulation in adult life. There are always aspects that need to be considered when interpreting the results. Confounders such as infections and stress might predispose subjects to unfavorable health outcomes similar to those caused by the famine itself. In the study by Li et al., it is difficult to differentiate between the effect of stress and that of malnutrition. Therefore, we have to ask whether the famine really is the underlying cause of the outcomes reported. Prenatal stress is known to affect the hypothalamic-adrenal-pituitary (HPA) axis and primarily cortisol secretion. This could be one plausible mechanism explaining the association between prenatal programming and a higher prevalence of hyperglycemia in adult life.

This increased risk observed among those exposed to famine during prenatal life was modified by adult dietary patterns and adult BMI. Obesity is one major risk factor for type 2 diabetes. The combination of a small body size at birth and later overweight or obesity increases the risk for type 2 diabetes markedly (12). In other words, a mismatch between birth size and the obtained adult body size seems to be an even stronger risk factor than obesity and birth size alone. However, data on body size at birth was unfortunately not available to Li et al.

There was an increased risk of impaired glucose regulation among those children exposed to the famine in later childhood. The higher prevalence of hyperglycemia could be due to the fact that this group was older. This finding might deserve some more attention. It is a well-known fact that not only prenatal factors influence later health, but also growth during infancy and childhood seem to have far-reaching health consequences (13,14). An unfavorable programming of body composition could be one mechanism linking early childhood growth with later increased risk for type 2 diabetes (15). Also, stressful events during childhood seem to influence health in later life. The prevalence of cardiovascular disease and type 2 diabetes in later life among individuals exposed to traumatic separation in early childhood because of World War II was markedly increased. Cardiovascular morbidity was higher among the former war evacuees, and a significant difference in prevalence of type 2 diabetes was also observed (16). These effects were not explained by age or socioeconomic status. In other words, early life traumatic events may extend lifelong effects on health, and this aspect should be focused upon in more detail in future studies.

The literature on the developmental origins of health and disease is steadily growing. There are still issues that need to be focused on, some of them being the underlying mechanisms including hormonal resetting, epigenetic mechanisms, and genetic confounding. The potential underlying mechanisms explaining the early programming of adult health and disease are schematically presented in Fig. 1. These include maternal factors, placental function, genetic and epigenetic mechanisms, as well as a large number of other factors. These factors could program organ and body function and composition as well as hormonal and growth factors. Within the context of type 2 diabetes, the factors could have an effect on insulin sensitivity and secretion, on hepatic glucose production,

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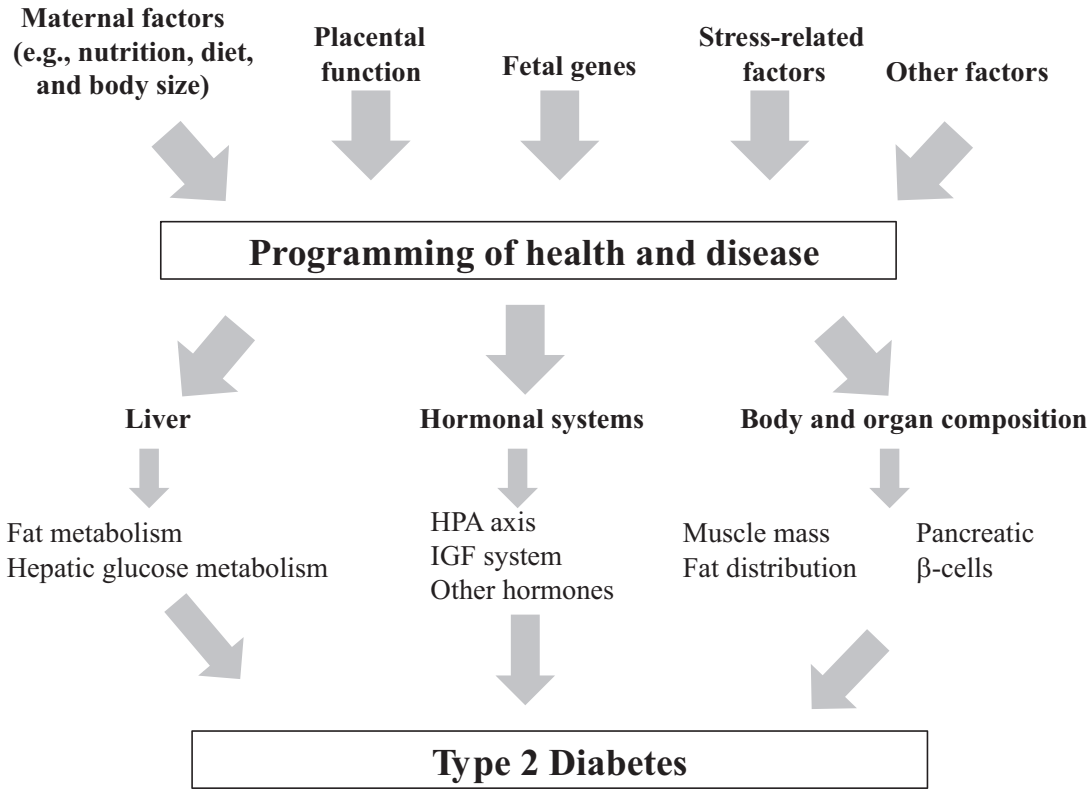

FIG. 1. Underlying factors associated with early programming of health and disease.

and on hormones involved in glucose and insulin metabolism.

During the past decade, we have learned that adult noncommunicable diseases are associated with different patterns of early growth. Importantly, from a public health point of view we should remember that adult diseases are not programmed, but the tendency toward these unfavorable health outcomes does seem to be programmed. The early life risk factors are largely modifiable by later lifestyle, and obviously lifestyle matters from the cradle to the grave. Ensuring the optimal health of women of reproductive age will have long-term health consequences for their offspring.

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